

Dispelling the Myths: Treatment of Patients with Ischemic Heart Disease and Left Ventricular Dysfunction

Based on a presentation by Stephen S. Gottlieb, MD

Presentation Summary

It is well known that beta-blockers are indicated for patients post-myocardial infarction (MI), and that post-MI patients who receive them live longer than those who do not. Yet only a third of post-MI patients are given beta-blockers. Much high-quality data supports the efficacy of beta-blockers and angiotensin converting enzyme inhibitors in the management of the patient with ischemic heart disease and left ventricular dysfunction.

Patients who do receive beta-blocker therapy tend to be healthier, in terms of heart function and disease state, than those who do not. But, it is the least healthy post-MI patients who stand to benefit the most in terms of improved survival, from beta-blocker therapy. A

1992 meta-analysis that examined outcomes associated with various antihypertensive medications showed that beta-blockers were among the drugs causing quality-of-life problems, including sexual dysfunction and deleterious effects on well-being and sleep. This may account in part for why beta-blockers are not more frequently used after an MI. But this analysis also showed that the degree of these effects was small. The frequency of adverse quality-of-life effects also appears exaggerated as none of them reached statistical significance.

Evidence also supports the idea that beta-blockers may be a more appropriate first-line therapeutic choice for post-MI patients than are the more commonly used calcium channel blockers.

How should the patient with both ischemic heart disease and left ventricular (LV) dysfunction be treated? Most of the data on such

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patients have been obtained from studies of patients post-myocardial infarction (MI). Examining these studies suggests that many current treatment practices in this patient population may be incorrect, according to Stephen S. Gottlieb, MD, Associate Professor of Medicine, University of Maryland School of Medicine in Baltimore.

For example, practice surveys show consistently that over the past several years, about one third of patients for whom beta-blockers are indicated, actually receive these agents. Another third receive calcium channel blockers. "Patients with MI and an ejection fraction of less than 40% should be given angiotensin converting enzyme (ACE) inhibitors; only 60% are," said Dr. Gottlieb. "Furthermore, about 67% of patients who should be receiving aspirin actually receive aspirin. What factors account for these figures?"

Inadequate Use of Beta-Blockers

Dr. Gottlieb said it is well known that beta-blockers are indicated for patients post-MI, and that the patients live longer

if they are given these agents than if they are not. Despite this understanding, however, only one third of patients receive beta-blockers after MI. Patients in this group largely are the healthier ones, suggesting that physicians prefer to start therapy with beta-blockers in patients in whom there are no contraindications.

But it is the least healthy post-MI patients; those with the poorest LV function and a history of congestive heart failure (CHF), who stand to benefit the most, in terms of improved survival, from beta-blocker therapy. "This is regrettable," Dr. Gottlieb said, "because the patients who are likely to benefit the most—that is, sick patients—are not being treated with beta-blocker therapy."

Beta-blockers are also not being used widely enough for patients who have ischemic heart disease with other non-cardiac complications. One such complication is coexisting diabetes. Examination of survival curves for post-MI patients with and without diabetes, some of whom were treated with beta-blockers and some of whom were not, shows that beta-blocker treatment improved survival in both groups. "I do not believe diabetes is a contraindication to the use of beta-blockers in patients with coronary artery disease," Dr. Gottlieb said.

A frequently expressed concern, Dr. Gottlieb said, relates to beta-blockers and pulmonary disease. These agents clearly are contraindicated in patients with asthma. However, the clinician must make a distinction between asthma and chronic obstructive pulmonary disease (COPD). Patients with MI tend to be older than non-MI patients and are likely to be smokers. They have COPD, rather than reactive airways. A study with the brief-acting beta-blocker esmolol in patients with COPD showed that the pulmonary parameters of forced vital capacity and forced 1-second expiratory volume were not affected adversely by this agent.

In a second phase of the study, the investigators gave chronic beta-blocker

therapy to the patients with COPD. Although the condition of some patients deteriorated, the researchers were able to predict the patients in whom deterioration occurred. Patients who had reactive airways (that is, a response to albuterol)

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and a history of wheezing had a 50% chance of deteriorating. Those who had only one of these risk factors had about a 15% chance. Among those who had neither risk factor, none deteriorated. "I believe that COPD is not a contraindication to beta-blockade in a patient whose cardiac disease is a strong indication for beta-blockers," Dr. Gottlieb said.

Another issue that needs to be reevaluated, Dr. Gottlieb noted, is the effect of beta-blocker treatment on the quality of patients' lives. A meta-analysis published in 1992 examined outcomes associated with administration of various antihypertensive medications—ACE inhibitors, beta-blockers, centrally acting agents, calcium channel blockers, diuretics, and other vasodilators. Beta-blockers were among the drugs causing quality-of-life problems, including sexual dysfunction and effects on well-being and sleep. In all instances, however, the degree of these effects was not large. The analysis seemed to show little deterioration in mood resulting from medication administration; in fact, in some cases, mood improvement occurred.

The study also showed that the frequency of adverse quality-of-life effects has been exaggerated, as none of the differences reached statistical significance. "It would seem that the incidence of anecdotally reported effects of antihypertensive agents on quality of life exceeds that of real effects. I believe that the importance of the quality-of-life issue has been overestimated.

"How should all these findings be interpreted? Together, they suggest that beta-blockers should be the first-line choice for patients with ischemic heart disease," Dr. Gottlieb said.

What Is the Place of Calcium Channel Blockers?

A number of studies indicate that calcium channel blockers should not be used in patients post-MI. In a meta-analysis by

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Furberg, in *Circulation*, the risk ratio for mortality increased as the daily dose of short-acting nifedipine increased. The Multicenter Diltiazem Post-Infarction Trial (MDPIT) provides the strongest evidence supporting the contraindication of calcium channel blockers in these patients. In the MDPIT, patients with LV dysfunction did worse when given diltiazem than when given a placebo. Yet it is this patient group whose post-MI status is most precarious.

The Diltiazem Reinfarction Study (DRS) on non-Q-wave MIs appeared to show significantly better outcomes in diltiazem patients than in placebo patients. However, the test performed to determine statistical significance was an inappropriate one, according to Dr. Gottlieb. The study had only a 2-week follow-up period and was conducted at a time during which treatment of non-Q-wave infarcts was very different from what it is today. Therefore, the interpretation of the results of this trial remains unclear.

Dr. Gottlieb said that a study comparing nifedipine, isosorbide dinitrate, and the combination of the two agents, showed that nifedipine, alone or in the combination, increased symptoms, the number of episodes of CHF, and the number of hospitalizations. Calcium channel blockers also are known to be negative inotropes that cause deterioration of cardiac function.

"I personally have not seen any evidence to convince me that the calcium channel blockers are indicated in post-MI patients. However, they are being used in this patient population," said Dr. Gottlieb.

What Is the Place of ACE Inhibitors?

With the exception of the second Cooperative New Scandinavian Enalapril Survival Study (CONSENSUS II), all the studies have shown that patients with poor LV function should receive an ACE inhibitor. As long as blood pressure is adequate, according to Dr. Gottlieb, patients should be given this therapy early, as soon as they are hospitalized. "In the case of a post-MI patient without LV dysfunction, however, the indication for ACE inhibitor is less strong, and the physician may wish to consider using another drug," he noted.

Dr. Gottlieb added that contraindications to ACE inhibitors do exist, but are less prevalent than many physicians believe. Cough and rash occur in approximately 5% of patients. Although these side effects can be bothersome, neither is particularly dangerous. The cough, said Dr. Gottlieb, is influenced by the effect of the ACE inhibitor on bradykinin; taking one aspirin per day may eliminate it. Therefore, if a patient with severe CHF can tolerate a cough, ACE inhibitor therapy should be continued.

If dysgeusia occurs, ACE inhibitor therapy must be stopped. This contraindication is very rare.

The serious concern is that hypotension or renal failure may occur with ACE inhibitor use. Generally, ACE inhibitors cause these problems in patients who are intravascularly depleted, rather than in those who cannot tolerate the drug. For example, in a patient with heart failure who is intravascularly depleted, a diuretic will accelerate the renin-angiotensin (RAA) system so that this system maintains both the patient's blood pressure and renal function. Consequently, blocking the RAA system results in hypotension or renal failure. The solution, according to Dr. Gottlieb, is

not to stop ACE inhibitor therapy, but rather, to change the patient's fluid status. Decreasing the diuretic will permit the patient to regain more nearly normal fluid balance.

Asymptomatic low blood pressure is not necessarily hypotension, Dr. Gottlieb said. In a patient with acute MI, it probably is; in this case, blood pressure should not fall to 70 mm Hg because of ACE inhibition. In a more chronic setting, however, if the patient is accustomed to the low BP, the ACE inhibitor is still indicated.

Dr. Gottlieb believes there also are misperceptions with respect to ACE inhibitors and renal failure. As with hypotension, if renal failure is provoked by therapy, this effect can be offset by changing the patient's fluid status. A separate issue is the management of a patient whose renal function is poor even before therapy is begun. The data are very clear: Baseline renal function does not increase the risk of renal dysfunction with ACE inhibitor therapy. Renal dysfunction occurs when ACE inhibitors are given because of a hemodynamic effect, not because of the baseline glomerular filtration rate (GFR). Dr. Gottlieb said he was aware of a study that showed even patients with the worst GFRs could improve when given ACE inhibitors.

According to Dr. Gottlieb, a patient with a high creatinine should be watched carefully if given an ACE inhibitor. A serum creatinine of 3.0 mg/dL is not a reason, Dr. Gottlieb said, to withhold this therapy.

Conclusion: New Knowledge To Be Heeded

"I think we have held a lot of preconceived notions in the past. But now we have the data, and if we look at those data it's clear: we should be changing our practices," said Dr. Gottlieb.

"We can no longer ignore the fact that aspirin improves survival post-MI. We can no longer ignore the fact that lipid-lowering agents also improve survival. And comparable sizeable bodies

of high-quality data have established the places of beta-blockers and ACE inhibitors in the management of the patient with ischemic heart disease and LV dysfunction."

... GENERAL DISCUSSION ...

Question: You have made a general statement that calcium channel blockers should not be used in patients with coronary artery disease and left ventricular dysfunction. However, the third-generation dihydropyridines have shown some potential in this setting. Could you please comment?

Dr. Gottlieb: The question really concerns amlodipine and felodipine. Data indicate that they may be safe when compared with such agents as nifedipine (or the non-dihydropyridine diltiazem), which are clear negative inotropes. In the PRAISE study (Prospective Randomized Amlodipine Survival Evaluation), improvement after amlodipine therapy was observed only in patients with non-ischemic dilated cardiomyopathy. Patients with ischemic cardiomyopathy had no improvement (and no worsening). At this point, therefore, if we give amlodipine to treat coronary artery disease, we cannot claim that this will help the patient's ischemic heart disease or improve his chance of surviving. But perhaps we now have evidence that amlodipine and felodipine are not as bad as the older calcium channel blockers.

I begin treating a patient with ischemic heart disease by giving beta-blockers. There should not be any question about that course of action. If the patient is still symptomatic, and you think a calcium channel blocker might be useful, it might be reasonable to try amlodipine or felodipine. They are the only calcium channel blockers that I would consider administering in someone with LV dysfunction.

Question: I would take issue with another general statement, that post-MI,

all patients should be given a beta-blocker, even if they have CHF. Would you place any stipulations on that?

Dr. Gottlieb: The stipulation is that you have to be extremely careful. You do not begin giving beta-blockers at high doses in patients with CHF. In the sickest patients, you start with very low

doses of the beta-blocker, watch the patient very carefully, and titrate up very cautiously. Generally, the drug I first use in a post-MI patient is a beta-blocker. If the patient has very poor LV function, it is an ACE inhibitor. But my goal will always be to try to give that patient a beta-blocker—starting with minuscule doses.